

thrombomodulin can be found in the claims as filed originally. See also pg. 6, lines 1-4 and lines 16-19; pg. 7, lines 1-8; pgs. 8-9, bridging paragraph; pg. 17, lines 1-2; pg. 29, lines 10-13; and Example 9.

Claims 6, 8 and 9 have been further amended to improve claim clarity.

No new matter has been added has been added by virtue of the claim amendments.

Claims 1, 3-12, and 14-28 stand rejected under 35 USC §112, first paragraph, as not satisfying the written description requirement. Applicants respectfully traverse as follows.

As an initial matter, it would seem that the USPTO has not fully considered the specification. For instance, the position was taken on pg. 3 of the Action that:

However, the last paragraph of page 7 under the section of the Summary of the invention, and is the only time EPCR being mentioned in the section. It briefly states EPCR is an example for agents that increase APC, there is no teaching regarding the functional fragments of the EPCR.

Respectfully, this is not correct. Applicants' specification describes EPCR and functional fragments thereof throughout the Summary section including pg. 7, lines 24-30; pg. 8, lines 28-31; and pg. 10, lines 21-26 (referring also to Example 9). To the extent the USPTO has not had the opportunity to review the Summary section in any detail, such action is earnestly requested.

At pg. 3 of the Action, the USPTO alleged that Applicants' specification does not satisfy the written description requirement on grounds that it does not teach particular fragments of EPCR, NF-kB, and TM. Applicants respectfully point out that to the extent such information has not been provided, it is not needed to confirm compliance with the

written description requirement of §112 first paragraph. According to the Guidelines for Examination of Patent Applications Under 35 USC §112, 1¶, "Written Description Requirement (hereinafter "Guidelines"):

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, **as of the filing date sought**, applicant was in **possession** of the now claimed invention (citing *Vas-Cath, Inc.* 935 F.2d at 1563-64, 19USPQ2d at 1117).

See the Federal Register, Vol. 66, pp. 1099-1111, part IB at pg. 1105.

Thus, the appropriate inquiry is to confirm Applicants were in **possession** of the subject matter claimed **as of the application filing date**. The Guidelines are flexible and provide several ways in which possession of the claimed invention can be demonstrated as of Applicants' filing date:

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in **possession of the claimed invention**, i.e., complete or partial structure, other **physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between structure and function, or some combination of such characteristics**. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

Federal Register, ibid, part IIA at pg. 1106.

Indeed, the Federal Circuit has held that the written description requirement "may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention". See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In view of the specification, the pending claims fully satisfy the written description requirement set forth by the Guidelines and the Federal Circuit. Accordingly, there is no basis for the instant §112, first paragraph, as formulated.

For instance, and in addition to the support already mentioned in the prior response, pg. 17, line 13 to pg. 19, line 25 of Applicants' specification describe a variety of suitable TM molecules (full-length and suitable fragments) for use with the invention.

In particular, pg. 17, lines 13-18 discuss no less than ten (10) scientific and patent references that describe such molecules for use with the claimed invention.

See also U.S. Pat. No. 4, 912, 207 which according to the specification at pg. 17 discloses the human TM sequence as well as functional fragments thereof for use with the claimed invention.

Applicants' specification precisely defines the phrase "functional fragment" of TM at pg. 17, lines 26 to 30, for instance.

Additional full-length and function TM fragments for use with the claimed invention are described at pg. 18, lines 4-16 of the specification.

Still further TM molecules including functional fragments thereof are described at pg. 18, lines 18-28 for use with the claimed invention.

Applicants specification also describes a range of EPCR and NF- κ B inhibitor molecules that can be used with the claimed invention.

For instance, and as already pointed out, suitable full-length EPCR and functional fragments thereof are described at pg. 7, lines 24-30; pg. 8, lines 28-31; and pg. 10, lines 21-26 (referring also to Example 9).

Additional description of suitable full-length EPCR and functional fragments thereof can be found at pg. 20, lines 14-21 (providing reference to six scientific and patent references).

Importantly, the phrase "functional fragment" of EPCR is specifically described at pg. 20, line 28 to pg. 21, line 2 of Applicants' specification.

Preferred full-length and functional fragments of EPCR are provided at pg. 20, lines 4-29.

Full-length and functional fragments of NF-kB inhibitor are fully described at pg. 22, lines 5-24. The phrase "functional fragment" of NF-kB inhibitor is specifically defined at pg. 22, lines 21-24.

In view of Applicants' detailed description of suitable TM, EPCR, and NF-kB agents for use in the claimed method including fragments, it is not seen how the instant written description rejection can withstand scrutiny. Clearly, Applicants' have shown that they were in possession of the claimed invention as of the application filing date.

The Office took the position that the specification of U.S. Patent No. 4,912,207 (as cited at pg. 17 of the instant application) does not teach "the structural-functional relationship of the cDNA sequence and the function of TM fragment, or any consensus region that is crucial to the function of TM". To the extent the '207 patent does not provide that information, it is not be needed to obtain patent protection for Applicants'

invention. As discussed above, Applicants have provided more than ample description of TM, EPCR, and NF-kb inhibitor agents as well as provided examples of appropriate functional fragments of those agents.

It is also noted that at pgs. 3-4 of the Action, the Office cited various sections from the Revised Interim Guidelines. However, it is not clear why these guidelines were cited. There is insufficient discussion in the Action regarding them. Respectfully, mere reference to the guidelines without discussing why they are applicable is insufficient grounds to substantiate the instant written description rejection. Clarification is requested.

In view thereof, reconsideration and withdrawal of the instant written description rejection are respectfully requested.

Claims 1, 3-12 and 14-28 stand rejected under 35 USC §112, first paragraph, as not being enabled in view of the specification. Applicants respectfully traverse as discussed below.

As an initial matter, the USPTO took the position that "protein chemistry is one of the most unpredictable fields in biology" (citing the Bowie et al. and Rudinger references). Action at pg. 4. Assuming, *arguendo*, that the allegation is even true, it is not seen how the Office can also contend in the same Action that the invention is also obvious. See pgs. 12-13 of the Action. Clarification is requested.

Nevertheless, the specification fully satisfies the "how to make" and "how to use" requirement of the statute in view of the claimed invention.

For instance, the cited Bowie and Rudinger references are rather old and outdated with respect to the filing date of the instant case. They are simply not relevant as cited to the claimed invention. Even if they were relevant, information relating to three dimensional structure and function relationship of proteins (Bowie et al.) and peptide hormone function (Rudinger), as pointed out by the Office, is certainly not needed for a worker to make and use the invention as claimed.

Moreover, it is not seen how the single sentence cited from Rudinger (a reference now nearly almost 30 years old) can outweigh more recent advances in the field as discussed throughout Applicants' specification.

The instant specification provides more than ample disclosure about how to make and use the invention.

For instance, claims 1 and 24 recite use of an effective amount of nucleic acid that encodes at least one of EPCR, thrombomodulin, NF- κ B inhibitor; or a functional fragment thereof. Both the phrases "effective amount" and "functional fragment" are precisely defined by the specification, thereby allowing one to make and use the invention as claimed.

For instance, pg. 16 of the specification, lines 17-21, defines an "effective amount" of the nucleic acid to be used as providing at least 20% or more APC when compared to a suitable control as determined by what is referred to in the specification as a standard activated protein C assay. See pg. 19, lines 5-13 and Example 3 for more information about the assay.

The phrase "functional fragment" as it applies to EPCR, TM and NF-kB fragments is specifically defined at pg. 17, lines 26 to 30; pg. 20, line 28 to pg. 21, line 2; and pg. 22, lines 21-24.

Accordingly, and in view of the detailed information provided by the specification, a worker would know how to make and use the claimed invention. No undue experimentation would be required.

Applicants respectfully disagree with the Office citation of MPEP 2164.01 ("How to Use the Claimed Invention") as support for the instant enablement rejection. The cited portion of MPEP 2164.01 states that:

[w]hen a **compound or composition claim is limited by a particular use**, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (claiming a chimeric gene capable of being expressed in any cyanobacterium and thus defining the claimed gene by its use).

Respectfully, reliance on this part of MPEP 2164.01 (and the cited Federal Circuit decision included therein) is misplaced. None of the pending claims are product-by-process type claims that claim a gene or otherwise.

However, MPEP 2164.01 does require that if a statement of utility in the specification contains within it a connotation (ie. a suggestion or implication) of how to use, and/or the art recognizes standard modes of administration are known and contemplated, then 35 USC §112 is satisfied.

Applicant's specification fully satisfies the requirement set forth by MPEP 2164.01. For instance, and as discussed throughout the specification, the claimed methods can be used to prevent or treat grafts from failure.

At pgs. 6-7 of the Action, the Office cited 35 USC §112, first paragraph, as taken from MPEP 2106B.2. Applicants note that MPEP 2106 is entitled "**Patentable Subject Matter- Computer-Related Inventions**". The claimed invention is not a computer nor is it a related device. Instead, Applicants are claiming specific treatment methods. It is not seen how reference to MPEP 2106B.2 (and particularly the portions underlined in the Action at pg. 7) is relevant to the rejection. Clarification is requested so that Applicants can respond.

Nevertheless, the instant specification fully satisfies the "how to make" and "how to use" requirement, especially as it applies to amended claims 1, 3-12 and 14-28.

For instance, claim 1 has been amended to point out that grafts are obtained from the same mammal subject to treatment. Dependent claims 3 and 4 provide for transplantation of treated grafts into the same mammal. Similarly, claim 24 has been amended to point out that grafts are obtained from the same mammal subject to graft engineering. Accordingly, concerns raised in the Action at pg. 7 (relating to allogenic and xenogenic graft failure) have been addressed.

At pg. 8 of the Action, the Office relied on MPEP 2164.05a by stating that "it is proper to use a post-filing art for the purpose of illustrating the levels of skill in the art". Generally however, MPEP 2164.05 provides that examiners should not use post-filing dated references to demonstrate that a subject application is non-enabling. A recognized exception is when individuals of skill recognize that the invention is not possible years after the filing date. MPEP 2164.05a. Respectfully, that narrow exception does not occur in this case.

As cited by the USPTO, the Kim et al. reference reports that:

Increased levels of TM and APC in Adv-TM transfected vascular graft did not result in the reduction in neointimal formation. In view of such, the invention

does not appear to be enabled absence of clarification of the contradictory evidence found in the references.

See the Office Action dated August 14, 2002 at pg. 8.

Respectfully, Kim et al. has been taken out of context by the USPTO. Fairly read, the reference does not provide evidence, as required by MPEP 2164.05a, that the authors recognized that invention of claim 1 and 24 was not possible.

For instance, on pg. 210 of Kim et al., the authors report that local thrombin generation "does not seem" to promote vein graft neointimal formation. That result was viewed as "surprising" by the authors themselves in view of other work in the field. See pg. 211 of Kim et al., for instance. Moreover, nowhere does Kim et al as cited report or discuss the invention of claims 1 and 24. It is not seen how the Office can contend that Kim et al. stands for an exception to the general rule that examiners should not use post-filing date references to substantiate a non-enablement rejection. MPEP 2164.05a.

Nonetheless, claims 1 and 24 have been amended to further prosecution with the Office. Specifically, the claims have been amended to recite use involving early graft failure.

In view thereof, reconsideration and withdrawal of the instant §112, first paragraph, rejection are respectfully requested.

Claims 1, 3-6, 8-12, 14-22, and 24-27 stand rejected as being anticipated under §102(e) in view of US Pat. No. 6,290,949 to French et al. While Applicants respectfully disagree with the rejection for reasons already of record, basis for it has been further addressed in this response.

In particular, claims 1 and 24 have been further amended to point out that if the agent used in the method is thrombomodulin, the featured nucleic acid must encode at least one other agent. See claims 1 and 24 as amended. Nowhere does the French patent as relied on in the rejection disclose a method for treating a vascular graft that involves introducing a nucleic acid that encodes thrombomodulin in combination with at least one of endothelial cell protein C receptor (EPCR) and NF- κ B inhibitor, for example. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 3-6, 8-12, 14-22, and 24-27 stand rejected as being obvious under §103 in view of US Pat. No. 6,290,949 to French et al. and US Pat. No. 6,309,380 to Larson et al. Applicants respectfully traverse for reasons of record and as discussed below.

The Office combination of the French and Larson patents is not the invention of claims 1 and 24 (as amended). According to the claims, when the administered agent is thrombomodulin, the featured nucleic acid must further encode at least one other agent as provided in the claims. None of the cited references when taken individually or together, provides any teaching, suggestion or motivation to perform the method for treating a vascular graft that involves introducing a nucleic acid that encodes thrombomodulin in combination with at least one of endothelial cell protein C receptor (EPCR) and NF- κ B inhibitor, for example.

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. 04-1105 should such fee be deemed necessary.

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Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 7 and 12 have been canceled.

Claims 1, 3, 4, 6, 8, 9 and 24 have been amended as follows:

1. (Amended) A method for treating a vascular graft of a mammal to resist early graft failure comprising,

a) introducing into cells of the graft from the mammal an effective amount of at least one nucleic acid encoding at least one of the following agents: endothelial cell protein C receptor (EPCR), thrombomodulin, NF- κ B inhibitor ; or a functional fragment thereof,

b) expressing the agent in the cells; and

c) increasing the APC sufficient to treat the graft, provided that when the agent is thrombomodulin, the nucleic acid further encodes [wherein] at least one of [the administered agents is] endothelial cell protein C receptor (EPCR), the NF- κ B inhibitor; or a functional fragment thereof, and step a) of the method is performed *ex vivo* or by direct injection into the graft.

3. (Amended) The method of claim 1, wherein the method further comprises transplanting the treated graft into the mammal [a host].

4. (Amended) The method of claim 1, wherein prior to step a) of the method, the graft is transplanted into the mammal [a host].

6. (Amended) The method of claim 3, wherein the transplanted vascular graft has sufficient APC activation as determined by a standard protein C assay to prevent or treat the early [or late] graft failure [as determined by a standard protein C assay].

8. The method of claim 6 [or 7], wherein the level of protein C activation as determined by a standard protein C detection assay [level] of the treated graft is at least about one order of magnitude higher than a control vessel [as determined by a standard protein C detection assay].

9. The method of claim 6 [or 7], wherein the increased protein C level of the treated vascular graft is detectable for at least about a week.

24. (Amended) A method for engineering a vascular graft of a mammal to resist early [that resists] failure, the method comprising:

- a) introducing into cells of the graft from the mammal an effective amount of at least one nucleic acid encoding at least one of the following agents: endothelial cell protein C receptor (EPCR), thrombomodulin, NF- κ B inhibitor; or a functional fragment thereof,
- b) expressing the agent in the cells; and
- c) increasing the APC in the graft sufficient to resist graft failure,

provided that when the encoded agent is thrombomodulin, the nucleic acid further encodes [wherein] at least one of [the administered agents is] endothelial cell protein C receptor (EPCR), NF- κ B inhibitor; or a functional fragment thereof, and step a) of the method is performed *ex vivo* or by direct injection into the blood vessel.